REMARKS

Upon entry of the present Amendment, claims 30-57 will be pending. Claims 1, 3-15, 18-24, 28 and 29 are withdrawn as directed to non-elected claims. Claims 2, 16, 17 and 25-27 are canceled and replaced with new claims 30-57. Applicant reserves the rights to pursue the withdrawn and/or canceled subject matter in a subsequent application.

Support for new claims 30 and 57 can be found throughout the application and, *inter alia*, in the original claims 2 and/or 16.

Support for new claim 31 can be found throughout the application and, *inter alia*, at page 11, lines 13-15 of the present specification.

Support for new claims 32 and 33 can be found throughout the application and, *inter alia*, at page 11, lines 17-19 of the present specification.

Support for new claim 34 can be found throughout the application and, *inter alia*, at page 11, lines 24-26 of the present specification.

Support for new claim 35 can be found throughout the application and, *inter alia*, at page 4, lines 4-7, page 4, lines 18-19, page 6, line 33 through page 7, line 23 and page 11, lines 24-26 of the present specification.

Support for new claim 36 can be found throughout the application and, *inter alia*, at page 4, lines 19-22 of the present specification.

Support for new claim 37 can be found throughout the application and, *inter alia*, at page 6, line 33 through page 7, line 23, page 18, lines 32-33 of the present specification and in original claim 23.

Support for new claims 38 and 39 can be found throughout the application and, *inter alia*, at page 4, lines 13-17, page 14, line 33 through page 15, line 2 and page 24, lines 2-5 of the present specification.

Support for new claims 40-42 can be found throughout the application and, *inter alia*, at page 15, lines 7-15 of the present specification.

Support for new claim 43 can be found throughout the application and, *inter alia*, in original claim 17.

Support for new claim 44 can be found throughout the application and, *inter alia*, at page 25, lines 9-29 of the present specification.

Support for new claims 45 and 46 can be found throughout the application and, *inter alia*, at page 6, lines 33 through page 7, line 5 and page 23, lines 25-31 of the present specification.

Support for new claims 47 and 48 can be found throughout the application and, *inter alia*, at page 25, line 35 through page 26, line 9 of the present specification.

Support for new claims 49-56 can be found throughout the application and, *inter alia*, at page 24, line 6 through page 25, line 3 of the present specification.

The above-described amendments do not introduce any new matter into the present application.

Restriction requirement

The Examiner alleges that this application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept.

I. Claims 1, and 3-5, drawn to a method of causing cardiomyocyte growth and/or differentiation using neuregulin (NRG), classified in class 514, subclass 2.

II. Claims 2, 16-17, and 25-29, drawn to a method of inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures, or cell-cell adhesions using NRG (or its derivatives), causing cardiomyocyte growth and/or differentiation, classified in class 514, subclass 2 (different process/search than Group I).

III. Claims 6-12, drawn to a method of identifying polypeptides or compounds which stimulate cardiac muscle cell differentiation using NRG and a test polypeptide or compound, classified in class 424, subclass 9.34.

IV. Claims 13-15, drawn to a method of identifying polypeptides or compounds which inhibit NRG stimulation of ventricular muscle cell differentiation, using a test polypeptide or compound, classified in class 424, subclass 9.34 (different process/search than Group III).

V. Claim 18, drawn to a method of preventing or lowering the incidence of heart disease in a mammal, comprising preventing or lowering the interference or effects of polypeptides or compounds on the action of NRG and its receptors, ErbBs, that produces heart failure, classified in class 424, subclass 1.69.

VI. Claim 19, drawn to a compound ("use of" unclear) that mimics the effects of neuregulin to treat or prevent PE, or IGF-1-mediated cardiac muscle cell dysfunction, classified in class 530, subclass 300+.

VII. Claims 20-21, drawn to a method of determining predisposition to heart disease or heart failure in a subject, comprising testing cardiac or related muscle cells of the subject for the ability to express and/or produce normal or adequate levels of neuregulin or its cognate ErbB receptors, classified in class 435, subclass 7.8.

VIII. Claims 22-23, drawn to a compound ("use of" unclear) of neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins in the treatment or management of heart disease and heart failure in a mammal, classified in class 530, subclass 300+.

IX. Claim 24, drawn to a compound ("use of" unclear) of neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins in the manufacture of a medicament for the treatment or management of heart disease and heart failure, classified in class 530, subclass 300+.

Applicant hereby confirms the previous oral election of Group II, claims 2, 16-17, and 25-29. Applicant respectfully submits Groups I and II can be searched in the same class and subclass, *i.e.,* class 514 and subclass 2. Accordingly, there is no additional search burden on the Examiner. Applicant respectfully requests Groups I and II be joined together. Applicant also respectfully requests Groups III and IV be joined together for the same reason. Applicant also respectfully requests Groups VI, VIII and IX be joined together for the same reason.

Rejections under 35 U.S.C. §112

Enablement

Claims 16-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating and/or reducing the risk of dissociation of cardiac muscle cell-cell adhesion and/or disarray of sarcomeric structures, via administering neuregulin, does not allegedly reasonably provide enablement for preventing dissociation of cardiac muscle cell-cell adhesion and/or disarray of sarcomeric structures using neuregulin.

This is rejection is rendered moot by the cancellation of claims 16 and 17.

Indefiniteness

Claims 2, 16-17, and 25-27 were variously rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, claim 16 is rejected for reciting "neuregulin or its derivatives."

This rejection is rendered moot by the cancellation of claim 16. In addition, the presently pending claims 30-57 recite the use of clearly defined neuregulin species, *i.e.*, a neuregulin protein, or a functional fragment thereof, or a nucleic acid encoding a neuregulin protein, or a functional fragment thereof. The meaning of a functional fragment of a neuregulin is well defined and well

known in the art as the characteristics and functions of a neuregulin, such as containing the EGF-like domain, activating the MAP kinase pathway and binding with ErbB2-ErbB3 or ErbB2-ErbB4 receptors are disclosed in the present specification and well known in the art. For example, it is known that the β2 domain of neuregulin 1 binds with ErbB2-ErbB3 or ErbB2-ErbB4 receptors to activate the MAP kinase pathway. In addition the β2 domain is well conserved in different types of neuregulin (*See e.g.*, Exhibit A, Holmes et al., *Science*, 256:1205-1210 (1992), at page 1206, Figure 2B showing the conserved region among HRG-α, HRG-β1, HRG-β2 and HRG-β3. Similarly, the function of the EGF-like domain is also well known. (*See e.g.*, Exhibit B, Chang et al., *Nature*, 387:509-512 (1997) at page 510, right column stating that the EGF-like domain neuregulins is sufficient for receptor binding and for stimulating cellular responses).

Claim 16 is also rejected for reciting "therapeutically effective amount" The Examiner acknowledges that neuregulin is a known cardiac muscle cell chemical with known activation mechanisms. Nevertheless, the Examiner alleges that what constitutes the "therapeutically effective amount" to carry out the level of remodeling or treatment (or prevention) or improvement of normal or diseased heart is unclear. Examiner also alleges that it was not found in the specification where this was tested and proven, defined, or described. The Examiner requests that applicant points out where in the specification such may be found, or distinctly claim the subject matter of what constitutes a "therapeutically effective amount."

This rejection is rendered moot by the cancellation of claim 16. The presently pending claims recite "an amount sufficient to activate the MAP kinase pathway in said cardiac muscle cells." Applicant respectfully submits that the phrase "an amount sufficient to activate the MAP kinase pathway in said cardiac muscle cells" is definite under the legal precedent.

The proper test for deciding whether the common phrase "an effective amount" is definite or not is whether or not one skilled in the art could determine specific values for the amount based on the disclosure. MPEP 2173.05(c) *citing In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA

1975). The phrase "an effective amount . . . for growth stimulation" was held to be definite where the amount was not critical and those skilled in the art would be able to determine from the written disclosure, including the examples, what an effective amount is. *In re Halleck*, 422 F.2d 911, 164 USPQ 647 (CCPA 1970). The phrase "an effective amount" has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. *In re Fredericksen* 213 F.2d 547, 102 USPQ 35 (CCPA 1954).

The presently pending claims specifically recite that the neuregulin, or a functional fragment thereof, is used at an effective amount for a specific function, *i.e.*, to activate the MAP kinase pathway in cardiac muscle cells. The present specification also teaches how to assess activation of the MAP kinase pathway, *e.g.*, by analyzing phosphorylation of MAP kinases in cardiac muscle cells, the expression of cell cycle inhibitor, p21, phenotypic organisation of contractile units, accumulation of contractile units, phenotypic alteration of cytoskeleton actin fibers, and the phenotype of cell-cell adhesions, etc (*See* page 4, line 31, through page 5, line 2 and page 17, line 1 through page 18, line 3 of the present specification). The present specification further gives exemplary effective amount, *e.g.*, at least 10^{-8} M (*See* page 6, line 33, through page 7, line 22 and in original claim 23). Thus, as in *In re Halleck*, those skilled in the art would be able to determine from the written disclosure, including the examples, what an effective amount is. The present claims are different from claims at issue in *In re Fredericksen* because the present claims specifically recite that the neuregulin, or a functional fragment thereof, is used at an effective amount for a specific function, *i.e.*, to activate the MAP kinase pathway in cardiac muscle cells.

Claim 25 is rejected for reciting "inducing expression of the gene(s) involved in neuregulin production." Claim 26 is rejected for reciting "produced by some other cell." Claim 27 is rejected for reciting for reciting "improved."

These rejections are rendered moot by the cancellation of claims 25-27.

It is respectfully submitted that the rejections of claims 2, 16-17, and 25-27 under 35 U.S.C. § 112 are overcome by the above remarks and/or amendments and must be withdrawn.

Rejections under 35 U.S.C. §102

WO 94/26298

Claims 2, 16-17, and 25-27 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by WO 94/26298.

WO 94/26298 is alleged to teach the use of neuregulin (and other related compounds/mimics), by contacting muscle cells (p. 3, lines 30-31), and specifically cardiac muscle cells (abstract; p. 3, line 17) and namely "any cell which contributes to muscle tissue" (p. 4, lines 17-18), in methods for normal and diseased hearts (p. 8-9) for "muscle regeneration" (p. 2, col. 12) in order to induce "both the proliferation of muscle cells and the differentiation and survival of myotubes" (p. 3, lines 15-17) and "the mitogenesis, survival, growth and differentiation of muscle cells" (p. 3, col. 26-29); wherein "[m]yogenesis . . . refers to any fusion of myoblasts to yield myotubes" [i.e. remodeling and increased cell-cell adhesion]. WO 94/26298 is further alleged to teach that administration if to a vertebrate, preferably a mammal (p. 4, line 5) and that "[n]euregulin effects on muscle may occur, for example, by inducing the synthesis of particular isoforms of the contractile apparatus such as the myosin heavy chain slow and fast isoforms; by promoting muscle fiber survival via the induction of synthesis of protective molecules such as, but not limited to, dystrophin; and/or by increasing acetylcholine receptor molecules at the neuromuscular junction (p. 4, lines 7-16) (see also claims, including nucleic acid (gene) stimulation).

Claims 2, 16-17, and 25-27 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. patent Nos. 644642 B1, 6087323 and WO 99/18976. U.S. patent Nos. 644642 B1, 6087323 and WO 99/18976 are alleged to teach the same invention elements as in WO 94/26298.

Applicant respectfully traverses the rejection. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. All presently pending claims require the use of a neuregulin protein, or a functional fragment thereof, or a nucleic acid encoding a neuregulin protein, or a functional fragment thereof, in an amount sufficient to activate the MAP kinase pathway in cardiac muscle cells. WO 94/26298 does not disclose or even mention MAP kinase pathway in cardiac muscle cells at all; let alone any teaching of using neuregulin in an amount sufficient to activate the MAP kinase pathway in cardiac muscle cells.

Indeed, WO 94/26298 teaches away from the presently claimed invention. As taught in the present specification:

> The higher ligand [neuregulin] concentration, concomitant with this increase in $p21^{CIPI}$ expression, resulted in a decrease in DNA synthesis, that was associated with terminal differentiation, whereas an increase in DNA synthesis and continued proliferation was observed with the lower dose (emphasis added).

(*See* page 6, lines 33 through page 7, line 5 of the present specification). In contrast, WO 94/26298 teaches the use of neuregulin at an amount that induces mitogenesis, and hence DNA synthesis. According to WO 94/26298:

> Products of this gene [neuregulin gene] have been used to show muscle cell mitogenic activity (see Examples 1 and 2, below), differentiation (Examples 3 and 6), and survival (Examples 4 and 5). This invention provides a use for all of the known products of the neuregulin gene (described herein and in the references listed above) which have the stated activities as muscle cell mitogens, differentiation factors, and survival factors.

(*See* WO 94/26298 at page 9, lines 14-21). In Examples 1-2 of WO 94/26298, which are used to show mitogenic activity, neuregulin is used at an amount to enhance cell proliferation and DNA synthesis (*See* WO 94/26298 at page 30, line 4 through page 32, line 20). Similarly, Examples 3-6 of WO 94/26298, which are used to show differentiation and survival enhancing activity, neuregulin is used at an amount to enhance cell proliferation and DNA synthesis. In Example 3, WO 94/26298

states "[t]he data in Fig. 2 demonstrate a large increase in the number of nuclei in myotubes when rhGGF2 is present, relative to controls" (*See* WO 94/26298 at page 33, lines 2-4). Similar disclosure is also found in Example 6 of WO 94/26298 (*See e.g.*, WO 94/26298 at page 36, lines 1-11, Table 3).

Another reason that WO 94/26298 does not disclose the presently claimed invention is that all presently pending claims require the use of neuregulin to induce remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions of cardiac muscle cells or to treat or delay disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures. WO 94/26298 does not disclose such a use of neuregulin. WO 94/26298, at most, discloses the use of neuregulin to enhance muscle cell proliferation and differentiation. According to the Examiner's own restriction requirement, however, a method of causing cardiomyocyte growth and/or differentiation using neuregulin (Group I) is patentably distinct from a method of inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures, or cell-cell adhesions using neuregulin (Group II).

WO 94/26298 does not anticipate certain dependent claims for additional reasons. For example, WO 94/26298 does not anticipate claims 31-33, 36 and 45-48 for not disclosing the additional requirements of these claims.

WO 99/18976 is also asserted as a prior art under 35 U.S.C. § 102(e). Revised 35 U.S.C. 102(e) allows the use of certain international application publications as prior art under 35 U.S.C. 102(e) as of their respective U.S. filing dates, including certain international filing dates. The prior art date of a reference under 35 U.S.C. 102(e) may be the international filing date if the international filing date was on or after November 29, 2000, the international application designated the United States, and the international application was published by the World Intellectual Property Organization (WIPO) under the Patent Cooperation Treaty (PCT) Article 21(2) in the English language. Since WO 99/18976's international filing date is October 8, 1998, which is earlier than

the November 29, 2000 date, WO 99/18976 does not qualify as a prior art under 35 U.S.C. § 102(e). In addition, the international publication date of WO 99/18976 is April 22, 1999, later than December 21, 1998, the priority date of the present application, WO 99/18976 does not qualify as a prior art under 35 U.S.C. § 102(a).

Even assuming, *arguendo*, that U.S. patent Nos. 644642 B1, 6087323 and WO 99/18976 are prior art to the present application, these cited references do not anticipate the presently pending claims for the same reasons that WO 94/26298 does not anticipate the pending claim.

Balligand

Claims 2, 16-17 and 25-27 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Balligand et al. (Jan./Feb.), 1997; 3(4):351-360) (Balligand). Balligand is alleged to teach the use of neuregulin, as a paracrine/autocrine acting trophic factor synthesized and released by cardiac myocytes and/or endothelial cells (p. 351, 1st ¶); in cardiac endothelium and tissue growth, and specifically regulation of cardiac myocyte growth (in the developed myocardium; page 354, 2nd ¶) as well as vasculogenesis and angiogenesis, and in the function of cardiac muscle following development (abstract).

Applicant respectfully traverses the rejection. First, Balligand is not citable under 35 U.S.C. § 102(e) as it is not an issued U.S. patent, nor a published U.S. application, nor a published PCT application.

Even assuming, *arguendo*, that Balligand is prior art to the present application, Balligand does not anticipate the presently pending claims. As discussed above, all presently pending claims require the use of a neuregulin protein, or a functional fragment thereof, or a nucleic acid encoding a neuregulin protein, or a functional fragment thereof, in an amount sufficient to activate the MAP kinase pathway in cardiac muscle cells. Balligand does not disclose or even mention MAP kinase

pathway in cardiac muscle cells at all; let alone any teaching of using neuregulin in an amount sufficient to activate the MAP kinase pathway in cardiac muscle cells.

Another reason that Balligand does not disclose the presently claimed invention is that all presently pending claims require the use of neuregulin to induce remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions of cardiac muscle cells or to treat or delay disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures. Balligand does not disclose such a use of neuregulin. Balligand, at most, discloses the use of neuregulin in cardiac endothelium and tissue growth, and specifically regulation of cardiac myocyte growth. According to the Examiner's own restriction requirement, however, a method of causing cardiomyocyte growth and/or differentiation using neuregulin (Group I) is patentably distinct from a method of inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures, or cell-cell adhesions using neuregulin (Group II).

Balligand does not anticipate certain dependent claims for additional reasons. For example, Balligand does not anticipate claims 31-33, 36 and 45-48 for not disclosing the additional requirements of these claims.

It is respectfully submitted that the rejections of claims 2, 16-17, and 25-27 under 35 U.S.C. § 102 are overcome by the above remarks and/or amendments and must be withdrawn.

Rejection under 35 U.S.C. §103

Claims 2, 16-17 and 25-27 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over any of WO 94/26298, U.S. patent Nos. 644642 B1, 6087323, WO 99/18976 or Balligand.

The Examiner states that Applicant's claims do not expressly teach that the neuregulin is in any composition or pharmaceutical composition for use in the method of treatment; however, even if such were claimed, and not expressly taught by the references above, it would have been obvious

to one of ordinary skill in the art at the time the claimed invention was made to use a neuregulin composition/pharmaceutical composition (*even with other components*); because all the references teach that neuregulin is a known natural compound released within cardiac muscle tissue and known to function biologically, in an apocrine or paracrine manner by activation of the MAP kinase pathway in the cells, to induce remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures, or cell-cell adhesions, in normal or diseased hearts (or lacking thereof in the latter); or to treat disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures.

The Examiner alleges that from the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. The Examiner also alleges that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

This rejection is respectfully traversed. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. As discussed above in connection with the anticipation rejection, nowhere does any of the cited references teach or suggest the use of neuregulin in an amount sufficient to activate the MAP kinase pathway in cardiac muscle cells. Similarly, nowhere does any of the cited references teach or suggest the use of neuregulin to induce remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions of cardiac muscle cells or to treat or delay disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures.

It is respectfully submitted that the rejection of claims 2, 16-17, and 25-27 under 35 U.S.C. § 103 is overcome by the above remarks and/or amendments and must be withdrawn.

CONCLUSION

Applicant respectfully submits that the rejections under 35 U.S.C. §§ 102, 103 and 112 have been overcome by the above remarks and/or amendments. Early allowance of the pending claims 30-57 are earnestly requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 524012000200. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated:

Respectfully submitted,

By_____

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